The Presidential Commission for the Study of Bioethical Issues

Moral Science

Nelson Michael, M.D., Ph.D.
Member

Secretary's Advisory Commission on Human Research Protections

February 28, 2012

THE WHITE HOUSE

WASHINGTON

November 24, 2010

MEMORANDUM FOR DR. AMY GUTMANN
Chair, Presidential Commission for the Study of Bioethical Issues

SUBJECT: Review of Human Subjects Protection

Recently, we discovered that the U.S. Public Health Service conducted research on sexually transmitted diseases in Guatemala from 1946 to 1948 involving the intentional infection of vulnerable human populations. The research was clearly unethical. In light of this revelation, I want to be assured that current rules for research participants protect people from harm or unethical treatment, domestically as well as internationally.

I ask you, as the Chair of the Presidential Commission for the Study of Bioethical Issues, to convene a panel to conduct, beginning in January 2011, a thorough review of human subjects protection to determine if Federal regulations and international standards adequately guard the health and well-being of participants in scientific studies supported by the Federal Government. I also request that the Commission oversee a thorough fact-finding investigation into the specifics of the U.S. Public Health Service Sexually Transmitted Diseases Inoculation Study.

In fulfilling this charge, the Commission should seek the insights and perspective of international experts, including from Guatemala; consult with its counterparts in the global community; and convene at least one meeting outside the United States. I expect the Commission to complete its work within 9 months and provide me with a report of its findings and recommendations.

While I believe the research community has made tremendous progress in the area of human subjects protection, what took place in Guatemala is a sobering reminder of past abuses. It is especially important for the Commission to use its vast expertise spanning the fields of science, policy, ethics, and religious values to carry out this mission. We owe it to the people of Guatemala and future generations of volunteers who participate in medical research.

Two Reports

The President's Charge

Historical Investigation:

U.S. PHS STD Research in Guatemala 1946-1948

REPORT: September 2011

Contemporary Review:

Scientific studies funded by the U.S., domestically or internationally

- w/ International Research Panel (subcommittee)

REPORT: December 2011

Contemporary Project – Methods

- International Research Panel
  - 14 members; 10 countries
  - Three meetings in private session; proceedings and recommendations released for public comment August 30
- Human Subjects Research Landscape Project
- Input from other experts, stakeholders, public
  - 4 Public Meetings
    - March 1, 2011, Washington, DC
    - May 18-19, 2011, New York, NY
    - August 29-30, Washington, DC
    - November 16-17, Boston, MA
  - Over 300 public comments

Contemporary Project – International Research Panel

- Members hailing from around the globe

John Arras (US)*	Julius Ecuru (Uganda)
Christine Grady (US)*	Dirceu Greco (Brazil)
Amy Gutmann (US)*	Unni Karunakara (India/US)
Nandini Kumar (India)	Sergio Litewka (Argentina/US)
Luis López (Guatemala)	Adel Mahmoud (Egypt/US)
Nelson Michael (US)*	Peter Piot (Belgium)
Huanming Yang (China)	Boris Yudin (Russia)

** Commission member*

International Research Panel Recommendations

1. Researchers must demonstrate respect for human subjects and their communities in all phases of clinical trial design and implementation. Recognizing other cultural standards and practices through community engagement is one concrete means of showing respect.
   - Ongoing international dialogue between U.S. and international bodies is critical to protecting human subjects in research.
   - U.S. and foreign investigators would benefit from clarification of the U.S. regulatory exception for foreign *"protections that are at least equivalent to those"* in the United States ("equivalent protections") found at 45 C.F.R. § 46.101(h) and how it can be applied.
2. Funders of human subjects research should support ethics training for investigators and others, including IRB members.

International Research Panel Recommendations

3. Greater efforts are needed to enhance transparency, monitor ongoing research, and hold researchers and institutions responsible and accountable for violations of applicable rules, standards, and practices. To enhance transparency and accountability, governments should consider requiring all greater than minimal risk research to be registered and results reported.
4. The United States should implement a system to compensate research subjects for research-related injuries.
5. Continued efforts to harmonize and guide interpretation of rules should be made a priority over creating new rules.

Human Subjects Research Landscape Project – Information Needs to Answer the President's Charge

- No systematic data are available across all federal agencies and departments supporting scientific studies with human subjects, e.g.,
  - Number of studies
  - Location of studies, and
  - Federal investment
- Limited systematic information is available about the extent to which regulations and standards guard the health and well-being of participants.

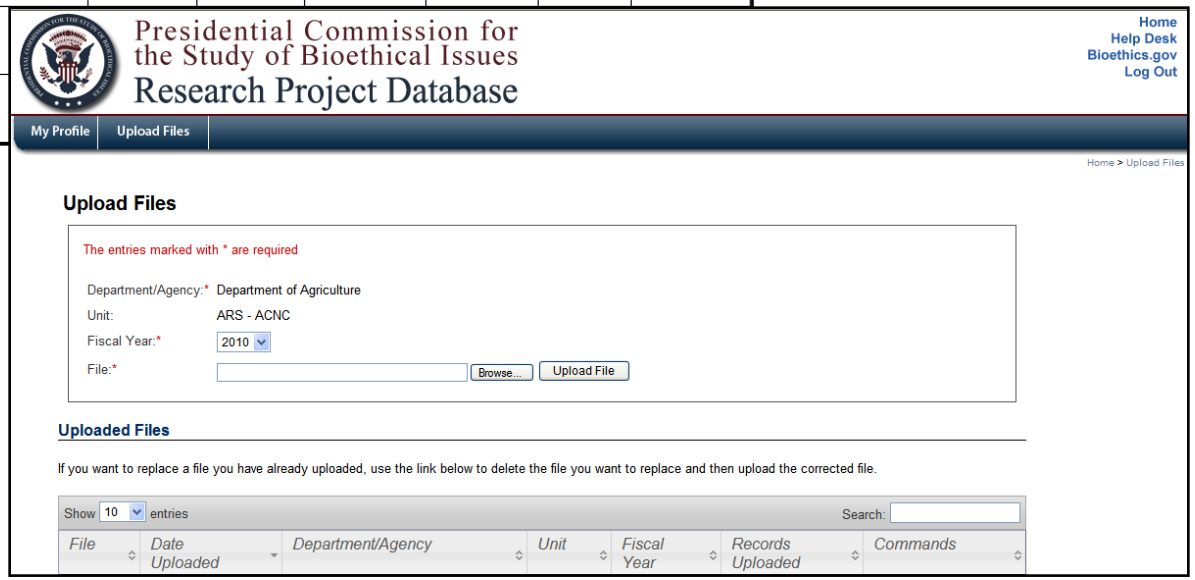
Human Subjects Research Landscape Project – Research Project Database

Research Project Database

To paste data into a cell when using Microsoft Excel 2010, right click the mouse in the cell and select the paste "Match Destination Formatting" option.
Please note that you CAN NOT use the Ctrl-V pasting method because it will erase the validation.

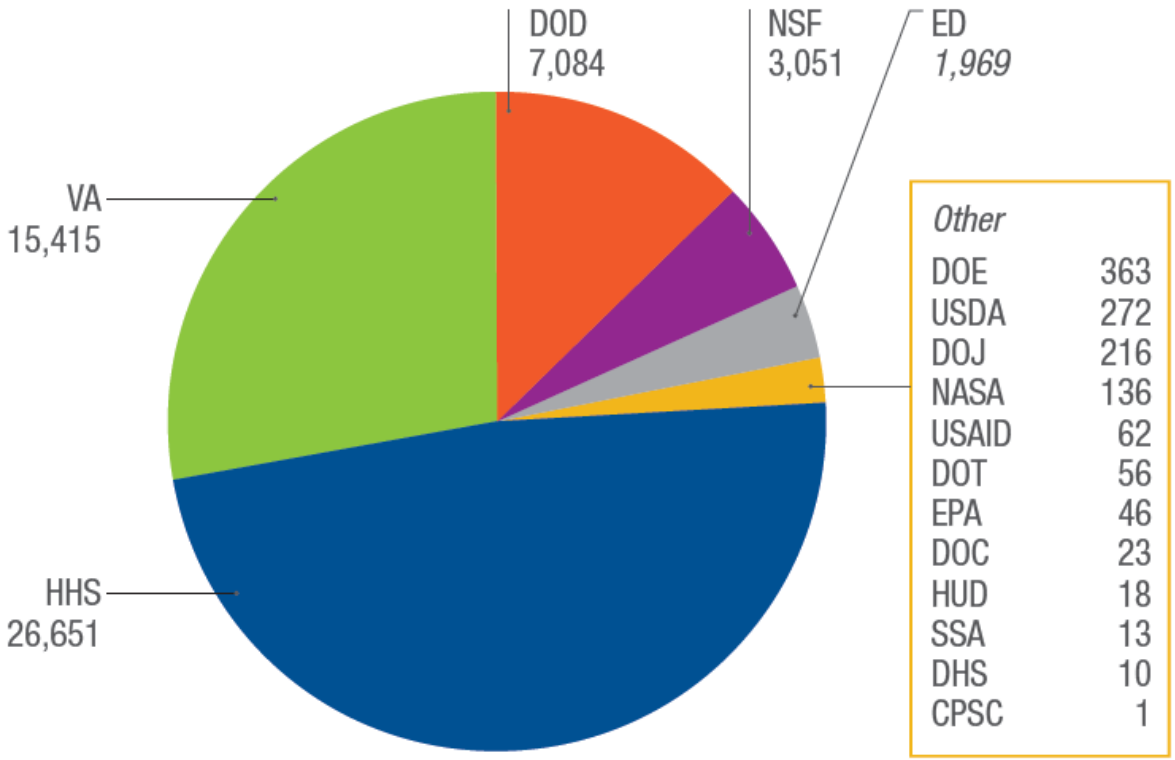
Study ID#	NCT# [N/A is option]	Title of Study	Abstract [N/A is option]	PI(s)	Year X of Y X [N/A is option]	Year X of Y Y [N/A is option]	Exempt or Non-Exempt [Ex/N] [N/A is option]	Total # of Sites [N/A is option]	ARRA Funded by Reporting Entity? [Y/N]	Other Fed Funding? [Y/N] [N/A is option]	Other Non- Funding [Y/N] [N/A is opt

- Project Name
- Identifier
- Funding
- Country Locations
- # Human Participants



HUMAN SUBJECTS RESEARCH LANDSCAPE PROJECT – RESULTS

Human Subjects Projects by Department/Agency, FY10†



† "Projects" include awards and individual studies. The CIA did not submit project-level data to the Commission's database because these data are confidential (although not classified). Departments/agencies that appear italicized reported that they were unable to provide complete data. See Appendix II for additional details.

Figure 2.2

HUMAN SUBJECTS RESEARCH LANDSCAPE PROJECT – RESULTS

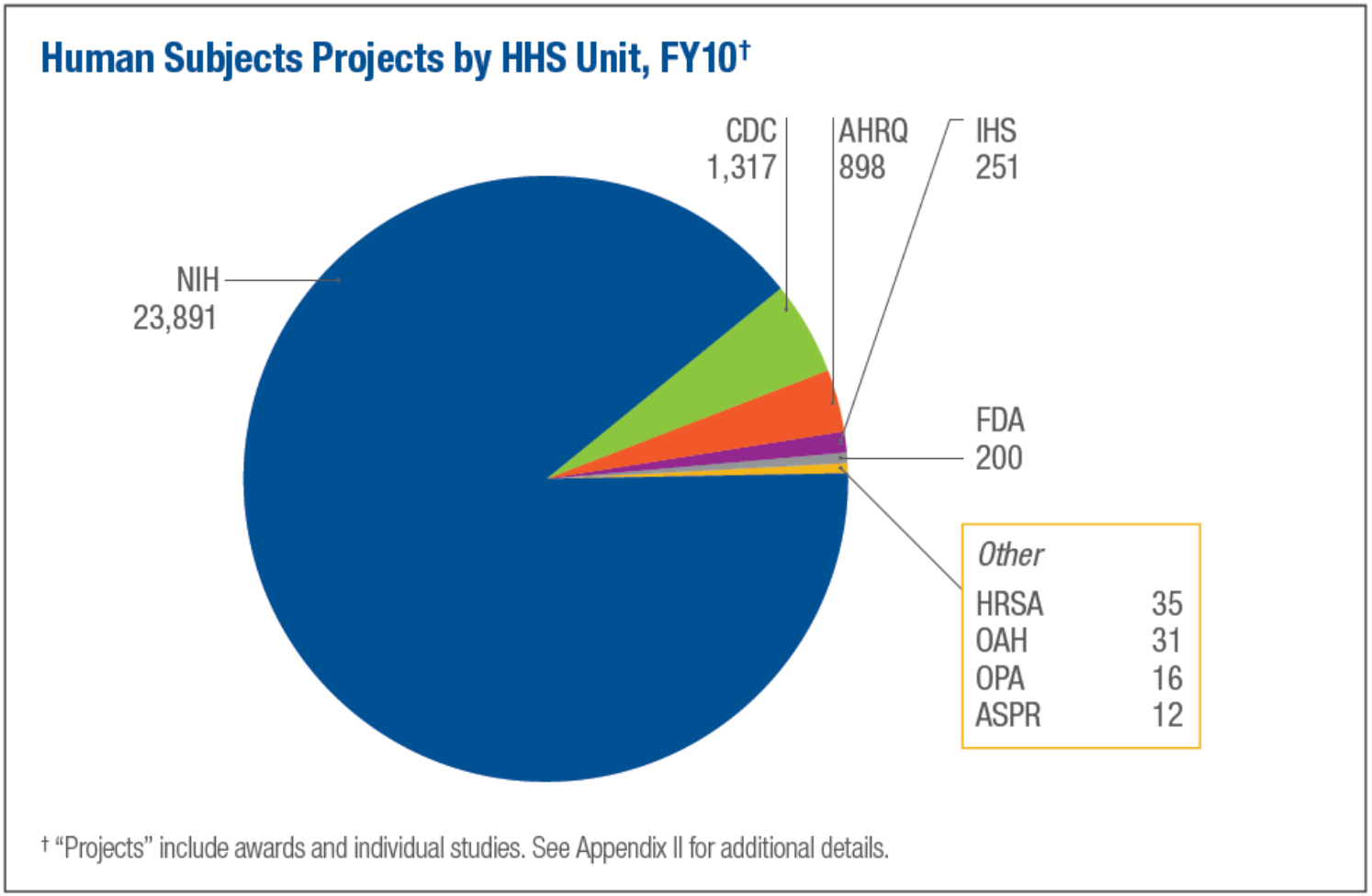
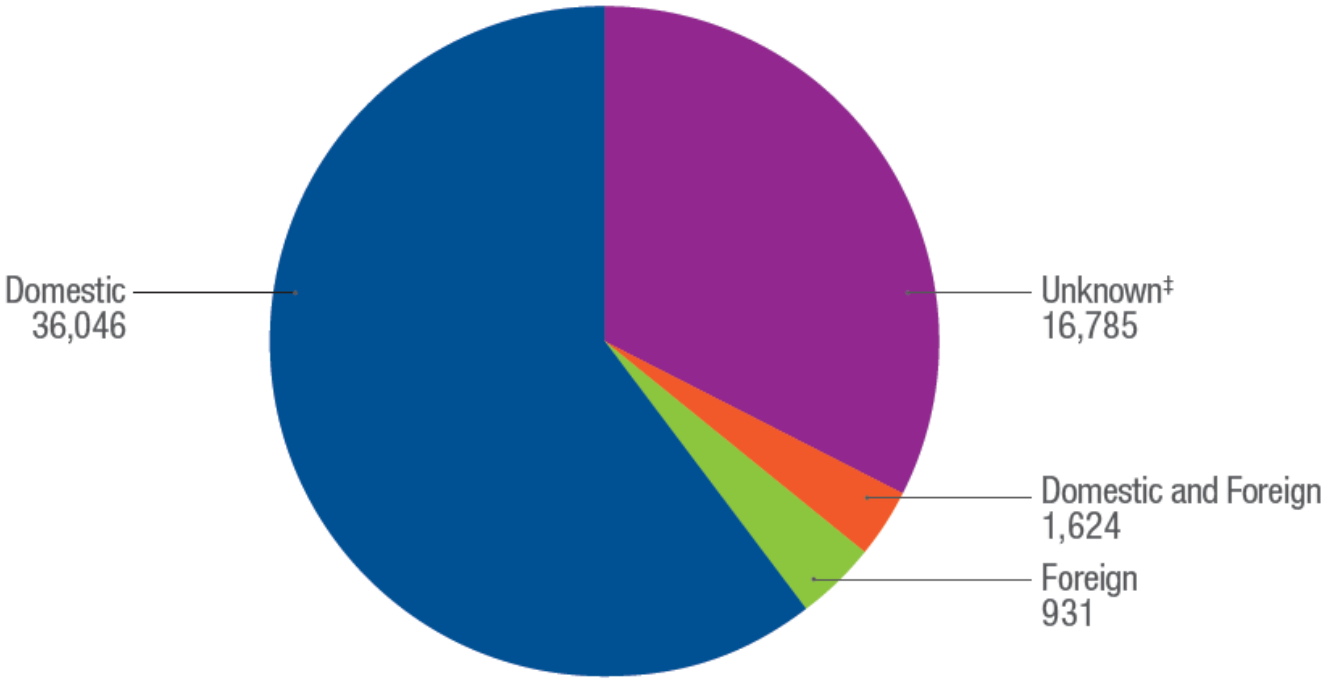


Figure 2.3

HUMAN SUBJECTS RESEARCH LANDSCAPE PROJECT – RESULTS

Human Subjects Projects by Location, FY10†



† "Projects" include awards and individual studies. The CIA did not submit project-level data to the Commission's database because these data are confidential (although not classified), but did indicate to the Commission that all of its human subjects research takes place in the United States. See Appendix II for additional details.

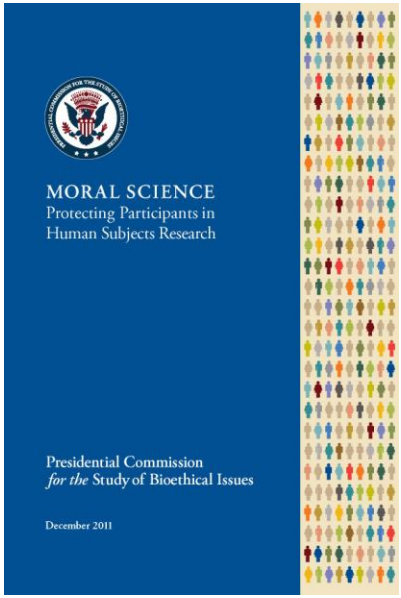
‡ Over 90 percent of "unknown" studies were reported by the VA, which explained that normally its human subjects research takes place in the United States.

Figure 2.4

Human Subjects Research Landscape Project – Summary Results

- Federal government supported tens of thousands of human subjects research projects every year
- These projects go well beyond biomedical research
- Internal agency systems are highly variable and many agencies could not readily provide all requested information
- Collecting such information is not a “magic bullet,” but it can provide insight into where to look to further to examine the ethics of research.

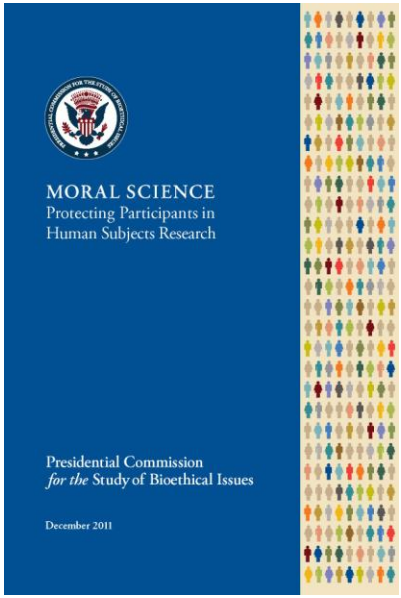
Findings – Overview



- The current U.S. system:
  - *Provides substantial protections for the* health, rights, and welfare of research subjects; and
  - *Serves*, *generally*, to "protect people from harm or unethical treatment."

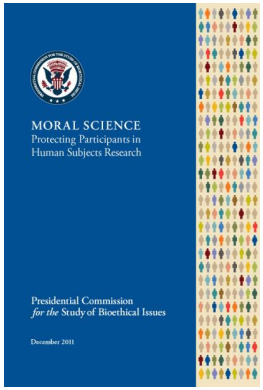
* But the currently limited ability of *some* governmental agencies to identify basic information research qualifies this conclusion.

Findings – Overview



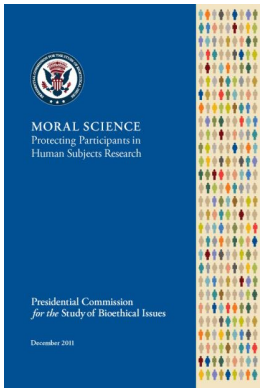
- Immediate changes can be made to:
  - increase accountability and
  - reduce the likelihood of harm or unethical treatment.
- The same *ethical principles* that apply to domestic research should also be applicable on the international front.
- 14 specific recommendations offered.

Recommendation 1: Improve Accountability through Public Access



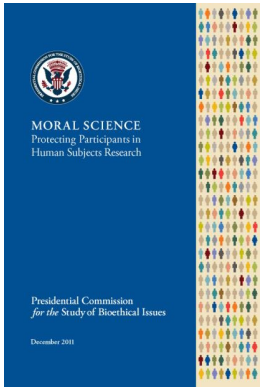
- Increase accountability through online access to basic human subjects research data:
  - Flexible strategies can be employed;
  - Minimum data set: title and investigator, location, and funding;
  - Portal through OHRP?

Recommendation 2: Improve Accountability through Expanded Research



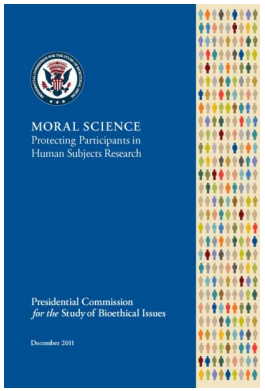
- All funders should:
  - Support the development of systematic approaches to assess the effectiveness of human subjects protections; and
  - Expand research related to ethical and social consideration of human subjects protection.

Recommendation 3: Treating and Compensating for Research-Related Injury



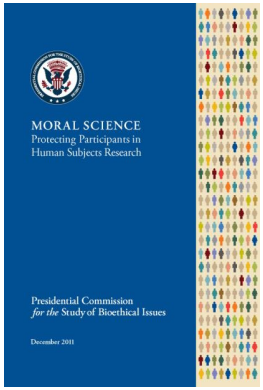
- An ethical condition for all human subjects research is that individuals should not be left alone to pay for the costs of treating injuries resulting directly from participation.
  - Almost all other developed nations endorse this principle.
  - The government has many tools in place now to do so.
- The government should *study research-related injuries* to determine if there is a need for a national system of compensation or treatment.

Recommendation 4: Treating and Compensating for Research-Related Injury Follow Up



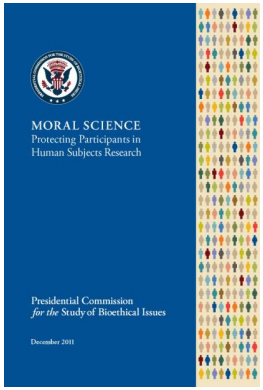
- Prior activities:
  - Many past bodies have called on the government to enact systems to protect subjects from bearing costs for injuries, e.g., the Radiation Commission, NBAC, President's Commission, and
  - The Government has considered this issue several times: HEW (1970s), HHS (2000s).
- The government should *publicly release* reasons for changing or maintaining the status quo regarding compensation or treatment for research-related injuries.

Recommendation 5: Make the Ethical Underpinnings of Regulations More Explicit



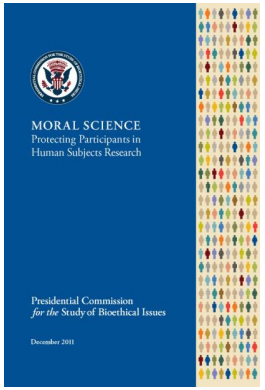
- Complaints about regulatory burden and compliance suggest that the *ethical* rationale for human subjects protections may be getting lost.
- The government should better explicate the ethical underpinnings for human subjects protection requirements to prevent erosion of respect for subjects.

Recommendation 6: Amend the Common Rule to Address Investigator Responsibilities



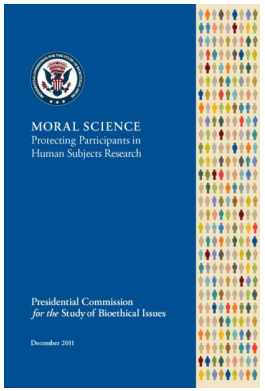
- Another way to ensure researchers understand their duties to respect patients:
  - Add responsibilities of investigators to the Common Rule and related agency requirements.
  - May also harmonize better with FDA and international rules, e.g., ICH-GCP.

Recommendation 7: Expand Ethics Discourse and Education



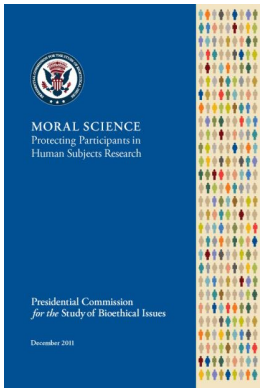
- Another way to ensure ethical treatment:
  - Universities, professional societies, licensing bodies, and journals should adopt more effective ways of integrating personal responsibility into professional research practice, including expanding ethics education.

Recommendation 8: Respect Equivalent Protections



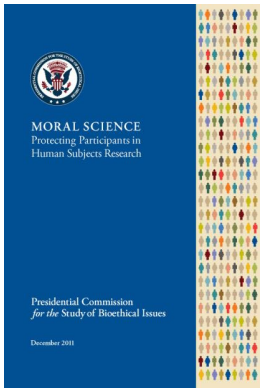
- International researchers receiving U.S. funds must comply with all U.S. procedural requirements, even when local laws offer greater protections for human subjects.
- The Commission recommends that the government:
  - Adopt or revise the 2003 Department of Health and Human Services Equivalent Protections Working Group's analysis, and
  - Develop a process for evaluating requests from foreign governments and other non-U.S. institutions for determinations of equivalent protections.

Recommendation 9: Promote Community Engagement



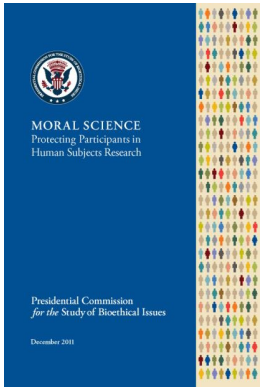
- The International Research Panel emphasized the need for community engagement and the Commission agreed.
- Further operational guidelines are needed.
- The government should:
  - Support further evaluation of models like the UNAIDS and AVAC Good Participatory Practice Guidelines to provide a standardized framework for community engagement practices across research fields.

Recommendation 10: Ensure Capacity to Protect Human Subjects



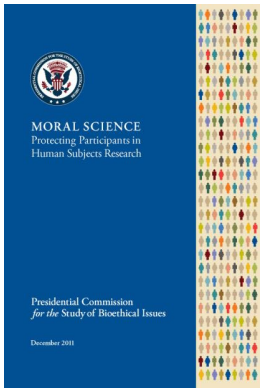
- Increasingly global human research means that some sites may not offer as robust a system of protections as the United States.
- An ethical condition of research is that sites have the capacity—or can achieve it while conducting the research—to protect human subjects.
- Government, and all funders:
  - Should ensure that researchers and proposed sites have the capacity to support protection of all human subjects.

Recommendation 11: Evaluate Responsiveness as a Condition for Ethical Site Selection



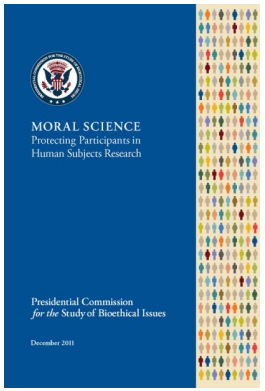
- Ensuring ethical site selection is more complicated than it may seem.
- The government should:
  - Support research to develop and evaluate justifications and operational criteria for ethical site selection.

Recommendation 12: Ensure Ethical Study Design for Control Trials



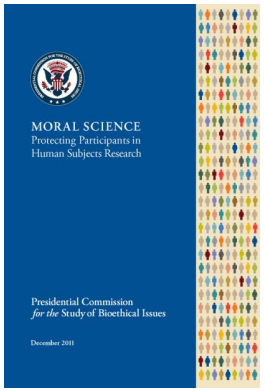
- Study Design for Control Trials is a long-standing concern.
- The Commission believes a middle ground, gaining currency in the last decade, offers an ethical solution. Control arm intervention may be other than the "best-proven" when:
    a) The "best-proven" intervention is not known to be the best for a particular population; and
    b) The scientific rationale *and* the ethical justification for the study design have undergone careful review to ensure all of the following:
        – use of placebo or other comparators is limited in time;
        – subjects are carefully monitored;
        – rescue measures are in place; and
        – established withdrawal criteria exist for subjects who experience adverse events.

Recommendation 13: Promoting Current Reform Efforts



- Endorsing ANPRM ideas to:
  - *a)* *Re-structure research oversight* to appropriately correspond with the level of risk to human subjects;
  - *b)* *Eliminate continuing review* for certain lower-risk studies;
  - *c)* *Reduce unnecessary, duplicative, or redundant IRB review* in multi-site studies;
  - *d)* *Make available standardized consent form templates* with clear language;
  - *e)* *Harmonize the Common Rule and regulations of the FDA*, and require that all federal agencies conducting human subjects research adopt human subjects regulations that are consistent with the Common Rule; and
  - *f)* *Develop an interoperable or compatible data collection system* for adverse event reporting across the federal government.

Recommendation 14: Responding to Recommendations



- The changes proposed are not only needed, but achievable.
- At least some of these recommendations have been made before.
- To further public understanding of these issues, the Office of Science and Technology Policy or another appropriate entity or entities within the government:
  - *Should respond* with changes or, if no changes are proposed, reasons for maintaining the status quo with regard to the recommendations below.

Table 3.3 Recommendation Follow-Up Summary

RECOMMENDATION NUMBER†	SUMMARY	OFFICE
1	Increase accountability through online access to basic human subjects research data.	OHRP/all departments and agencies that support human subjects research
2	Support the development of systematic approaches to assess the effectiveness of human subjects protections and expand support for research related to ethical and social consideration of human subjects protection.	OHRP/all departments and agencies that support human subjects research
3	Study research-related injuries to determine if there is a need for a national system of compensation or treatment for research-related injuries because subjects harmed in the course of human research should not individually bear the costs of care required to treat harms resulting directly from that research.	OSTP/HHS
4	Publicly release reasons for changing or maintaining the status quo regarding compensation or treatment for research-related injuries.	OSTP/HHS
5	Explicate the ethical underpinnings for human subjects protection requirements.	HHS/OSTP
6	Add responsibilities of investigators to the Common Rule.	HHS/OSTP
8	Adopt or revise the 2003 Department of Health and Human Services Equivalent Protections Working Group's analysis and develop a process for evaluating requests from foreign governments and other non-U.S. institutions for determinations of equivalent protections.	OHRP
9	Support further evaluation of the UNAIDS/AVAC Guidelines to provide a standardized framework for community engagement practices across research fields.	OHRP
11	Support research to develop and evaluate justifications and operational criteria for ethical site selection.	OHRP/all departments and agencies that support human subjects research
13	Develop proposed regulations to reform the current Common Rule.	OSTP/OHRP
14	Follow up.	OSTP/other appropriate entity

† Listed here are recommendations directed to the federal government only.

Selected Media Coverage

REUTERS

U.S. panel raps how agencies handle human research

THE LANCET

Moral science and the Presidential Commission for the Study of Bioethical Issues

the Atlantic

Atlantic (USA)

Today in Research: The Need for Transparency in Human Trials

The Washington Post

Washington Post (USA)

Bioethics panel urges system to compensate those hurt in medical experiments

BMJ

BMJ 2011;343:d8239 doi: 10.1136/bmj.d8239 (Published 20 December 2011) Page 1 of 1

Details of federally funded studies should be available on web, US commission says

BNA

BNA's *Medical Research Law and Policy Report* (USA)

Human Subject Protection: President's Bioethics Advisers Say Rules Protect Subjects, but Urge Transparency

Government Response Thus Far

• OSTP briefing	December 2011
• Agency briefings	December 2011 to January 2012
• $1 million committed to evaluate proposed revisions to Common Rule	January 2012
• Ongoing review	

Additional Information

- Future meetings open to the public:
  - May 17, Washington, DC

- Next topics –
  a) *Genes to Genomes*
  b) *Development of medical countermeasures for children*
  c) *Neuroimaging and the Self*

- Comments? Address to: info@bioethics.gov